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FROM THE GENOME TO THE PHENOME AND BACK: LINKING GENES WITH HUMAN BRAIN FUNCTION AND STRUCTURE USING GENETICALLY INFORMED NEUROIMAGING

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Abstract—In recent years, an array of brain mapping techniques has been successfully employed to link individual differences in circuit function or structure in the living human brain with individual variations in the human genome. Several proof-of-principle studies provided converging evidence that brain imaging can establish important links between genes and behaviour. The overarching goal is to use genetically informed brain imaging to pinpoint neurobiological mechanisms that contribute to behavioural intermediate phenotypes or disease states. This special issue on "Linking Genes to Brain Function in Health and Disease" provides an overview over how the "imaging genetics" approach is currently applied in the various fields of systems neuroscience to reveal the genetic underpinnings of complex behaviours and brain diseases. While the rapidly emerging field of imaging genetics holds great promise, the integration of genetic and neuroimaging data also poses major methodological and conceptual challenges. Therefore, this special issue also focuses on how these challenges can be met to fully exploit the synergism of genetically informed brain imaging. © 2009 Published by Elsevier Ltd on behalf of IBRO.

Key words: brain mapping, genome, imaging genetics, neuroimaging, phenomics.

The marked advances in molecular genetics and neuroimaging have greatly facilitated experimental strategies that integrate molecular genetics and human brain mapping (i.e., imaging genetics) (Meyer-Lindenberg and Weinberger, 2006). The central motivation behind imaging genetics is to link individual variations in the human genome to structural and functional variation in brain systems (Hariri, 2009). A wide range of brain mapping techniques is available to pinpoint variations in brain function or structure that are associated with a distinct genotype including functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (MRI), electroencephalography, and positron emission tomography (PET) of brain metabolism or neurotransmission. The blood oxygen level dependent (BOLD) MRI method has had particular success as a sensitive means of detecting genotype specific differences in temporal–spatial patterns of brain activity (Hariri, 2009). These studies provided proof of principle that brain mapping can narrow the gaps in the causal chain from a given genetic variation to behaviour.

The present special issue provides an overview about how the "imaging genetics" approach can be applied to study how genetic variations in the human genome contribute to complex behaviours and brain diseases. This special issue reviews recent advances in the field and also identifies important methodological and conceptual challenges that remain unresolved.

HOW TO CAPTURE THE PHENOTYPE?

Recent years have witnessed a shift in focus from genomics to phenomics (i.e., the systematic study of phenotypes on a genome-wide scale). This shift was mainly prompted by the failure of genetic linkage and association studies to produce reliable or replicable linkage or association findings to the clinical phenotypes, like bipolar disorder or schizophrenia. The main reason for this is that clinically defined phenotypes are highly variable and there are inherent diagnostic uncertainties (Gottesman and Gould, 2003). The issue is further complicated by the likelihood that common brain diseases are likely composed of multiple etiologies appearing as a common clinical endpoint (Gottesman and Gould, 2003). At the same time, genetic screening at a genome wide scale has become widely available, and the costs of genotyping methods have markedly decreased.

The question how to effectively define promising phenotypes is highly relevant to the field of imaging genetics. In contrast to the relatively straightforward organized genome, the human phenome is a multidimensional search space with several neurobiological levels, spanning the proteome, cellular systems (e.g., signaling pathways), neural systems and cognitive and behavioural phenotypes (Fig. 1). In a clinical context, the definition of symptoms and syndromes adds to the phenomic complexity (Fig. 1).

In this issue, Bilder et al. (2009) develop a rational framework that facilitates prioritizing certain phenotypes. A

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Abbreviations: COMT, catechol-O-methyltransferase gene; DAT, dopamine transporter gene; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PD, Parkinson's disease; SNP, single nucleotide polymorphism.

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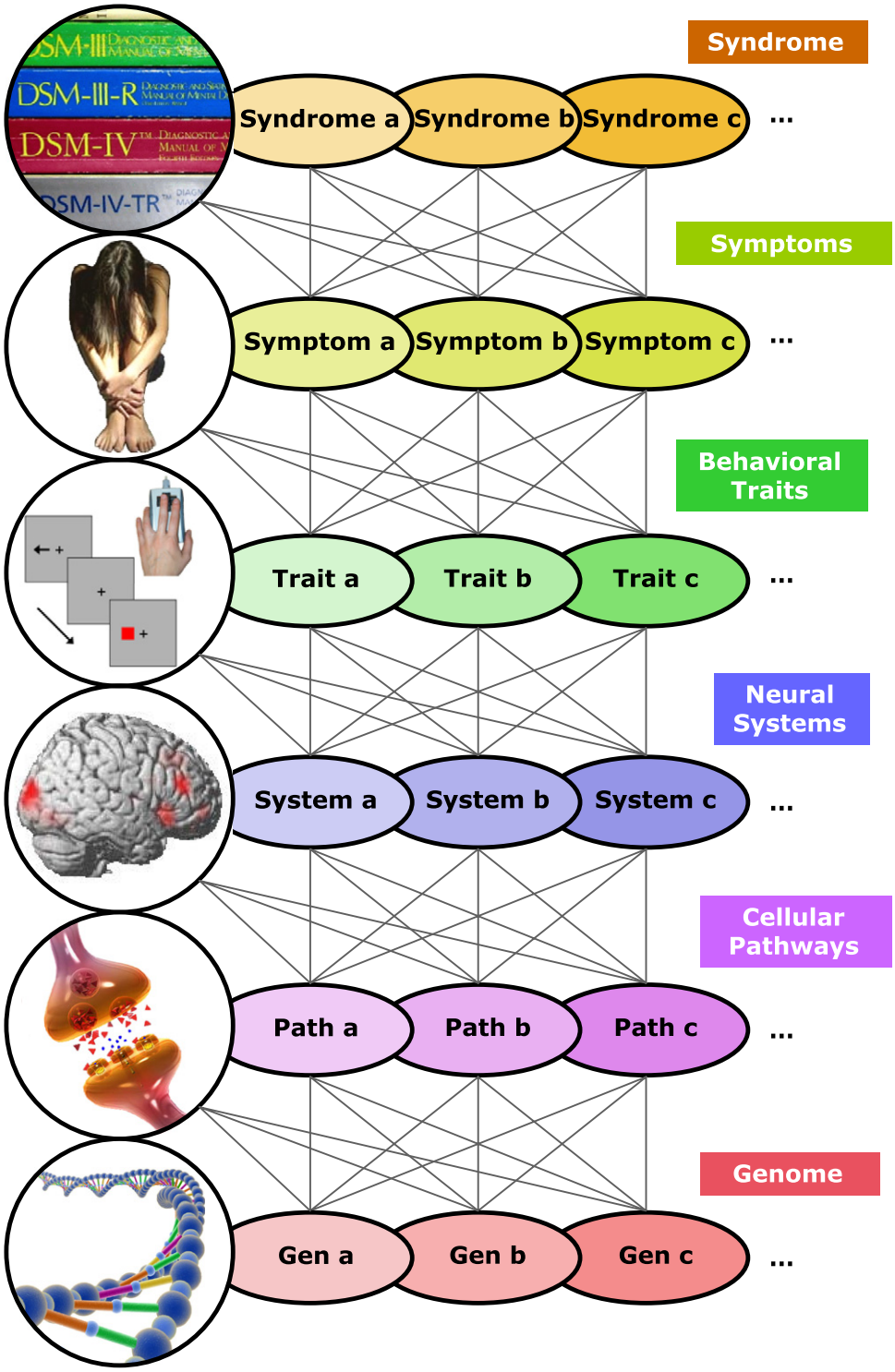

Fig. 1. A schematic framework for imaging genetics. Genetically informed neuroimaging needs to take into account the multiple neurobiological levels which link genome and phenome as well as the considerable overlap and interactions among neurobiological components at each level.

critical aspect in this framework not addressed by Gottesman and Gould (2003) concerns amenability of a phenotype for high throughput studies. This could be achieved for cognitive phenotypes by advances in psychometric theory, but also by improved Internet-based assessment. However, amenability for relatively high throughput phenotyping is certainly also an aspect to consider in future imaging genetics studies. To manage the complexity and facilitate systematic phenotyping, Bilder et al. (2009) propose a multi-layer schema reflecting the relationship of the

different levels of inquiry and biological scales which have to be integrated for a phenomics hypothesis. The challenges in defining appropriate phenotypes are also addressed in another paper which discusses how to build multi-level phenotype models of memory and intelligence (Sabb et al., 2009).

NEUROETHICAL CHALLENGES

Another, highly relevant perspective on the rapidly growing field of imaging genetics is the ethical challenges that accompany the combination of such powerful and sensitive approaches, i.e., neuroimaging and genetics in the study of psychiatric and neurologic disorders. Tairyan and Illes (2009) argue that these ethical challenges call for an expanded "neuro-space" in which societal and ethical values become closely and explicitly integrated with the new science. Crucial features of discriminative power within this new combined space concern the capacity to differentiate phenomena such as diseases. Cumulative power in the proposed neuro-space depends upon the ability to gain more in depth information about the discriminated phenomena and by extension, associated ethical challenges.

HOW TO ASSESS GENETIC VARIATION AND HEREDITABILITY?

A major research theme in the field of imaging genetics is to study how normal variations in the human genome are associated with complex behavioural traits and how these genetic variations modify the individual vulnerability to develop neuropsychiatric disorders (Hariri, 2009). In this framework, the term "genetic variation" usually refers to common variations in humans genes that exist in $>1\%$ of the population and impact the function of neuronal signaling pathways and brain circuits within the normal physiological range. This includes functional single nucleotide polymorphisms (SNPs), interactions among multiple SNPs (genetic networks), epigenetic factors, as well as copy number variations (i.e., insertions, deletions or duplications of relative large expansions of DNA). So far, imaging genetics has mainly adopted a hypothesis-driven approach focusing on common functional SNPs in candidate genes. Genome-wide association studies (GWAS), now including the identification of novel copy-number variants (CNVs), and closer examination of epigenetic regulation of expression (i.e., methylation) are being increasingly implemented in the research strategies of imaging genetics. It should be noted though that to date GWAS have been no more productive than genome-wide linkage studies revealing some hits (all of odds ratios <1.5) that are not being found across populations but not enough hits to explain complex illnesses. This indicates that small contributions from multiple genetic variants appear to be the rule rather than the exception. To disentangle the genetic architecture of complex behavioural traits and complex neuropsychiatric disorders, hypothesis-free screening of the human genome and hypothesis-driven research on genetic variations in candidate genes represent valid strategies providing complementary information at different levels.

Twin studies still represent the best approach to estimate the relative contribution of genetic factors to a given phenotype over shared environmental factors. In this issue, van't Ent et al. (2009) elegantly use functional brain imaging to dissociate genetically- and environmentally-mediated aspects of brain circuit function. They studied brain activity during a response interference task in monozygotic twins highly concordant or discordant for scores on the Child Behavior Check List attention problem scale where high scores are associated with the risk to develop attention deficit hyperactivity disorder. The use of between-subject comparison of high and low scoring concordant twins enabled them to identify a neuroimaging trait of attentional problems with a genetic basis. In contrast, the between-subject comparison of task-related activity in monozygotic twin pairs with discordant twin pairs allowed them to identify neuroimaging correlates of attentional problems attributed to environmental factors.

AN INTERACTIVE FRAMEWORK: GENE–GENE AND GENE–ENVIRONMENT INTERACTIONS

Several seminal studies have provided converging evidence that neuroimaging of individuals with a functional genetic polymorphism in a single candidate gene can offer important insights into the impact of that gene on brain circuit function and structure in healthy individuals (Hariri, 2009). This approach continues to provide important links between specific genes and behavioural phenotypes. In this issue, Dickinson and Elvevag (2009) review how the balance of dopamine in prefrontal cortex and related information processing is influenced by a functional Val158Met polymorphism in the catechol-O-methyltransferase (COMT) gene. Additionally, Frank and Hutchison (2009) present behavioural data showing that several striatal D2 receptor polymorphisms impact probabilistic avoidance learning. Yacubian and Büchel (2009) review the known genetic contributions to individual differences in reward processing and their link to addictive behaviour and social cognition. They refer to their recent work on epistatic interactions between two widely studied functional polymorphisms in the dopamine transporter (DAT) gene and COMT. Using fMRI, Yacubian and Büchel (2009) found that neuronal activity in the ventral striatum was influenced by distinct combinations of the DAT and COMT genotype, emphasizing the relevance of functional gene–gene interactions in genetic studies on reward processing. This notion is further corroborated in the paper by Hall et al. (2009) summarizing the effects of gene knockout (KO) of the DAT, the serotonin transporter and the norepinephrine transporter in KO mice on the behavioural effects of cocaine during conditioned locomotion. While the results confirm the central role of dopamine and DAT in the behavioural effects of cocaine, they also stress the polygenic basis of cocaine-mediated behaviour and the non-unitary nature of drug reward mechanisms. The issue of gene–gene interactions considerably adds to the complexity of imaging genetics. Gene–gene interactions pertain not only to genetic variations of different genes affecting the same or interacting

cellular pathways but may also occur in the presence of multiple functional variants in the same gene.

Similar to gene–gene interactions, gene–environmental interactions need to be taken into account in genetically informed neuroimaging studies. Presenting their work on a common functional polymorphism in the brain-derived neurotrophic factor (BDNF) gene, Casey et al. (2009) show genetic and environmental loadings on intermediate neuroimaging and behavioural phenotypes across development. They provide converging evidence that gene- and environment-related alterations in BDNF levels affect behavioural and neuroanatomical changes that evolve over time. Moreover, they propose that development trajectories may present new intermediate imaging phenotypes themselves. The importance of developmental aspects is also stressed in the contribution by Brocki et al. (2009) that focuses on developmental aspects in the genetic pathways of executive attention in the anterior cingulate cortex. Along the same lines, the contribution by Voelker et al. (2009) shows that parenting quality in early development modulates the genetic influence mediated by variations in COMT gene on attention.

COMPLEX BEHAVIOURAL TRAITS AND ASSOCIATED NEUROPSYCHIATRIC DISORDERS

The genetic study of complex behavioural traits continues to mature along with that of complex neuropsychiatric disorders. In this issue, a series of papers discuss the genetic contributions to complex behavioural traits, such as emotional regulation (Canli et al., 2009), anxiety (Norrholm and Ressler, 2009), executive attention (Brocki et al., 2009), pain processing (Ritter and Bingel, 2009) or motor control (Cheeran et al., 2009) with links to related disorders. Other contributions adopt a clearly clinical perspective with a primary focus on a wide range of complex neuropsychiatric diseases, including Alzheimer's disease (Reitz and Mayeux, 2009), major depressive disorder (Savitz and Drevets, 2009), bipolar disorder (Barnett and Smoller, 2009), schizophrenia (Bertolino and Blasi, 2009), attention deficit hyperactivity disorder (Plomp et al., 2009), autism spectrum disorders (Piggot et al., 2009), or epileptic syndromes (Siniatchkin and Koepp, 2009).

A concept central to all these lines of research entails the use of brain imaging to define intermediate phenotypes in living humans (Gottesman and Gould, 2003). These intermediate imaging phenotypes are state-independent hereditable traits providing quantitative measures of specific neurobiological mechanisms, for instance the temporal–spatial distribution of task-related neuronal activity within specific brain circuits. Compared to behavioural or syndromal phenotypes, intermediate imaging phenotypes may offer better mechanistic insights into how neural systems are affected by genetic variants and how this contributes to the emergence of neuropsychiatric disorders by virtue of their presumed closer proximity to gene expression. This special issue contains many illustrative examples for the diversity of structural, functional, and metabolic brain mapping methods that are currently applied to delineate intermediate imaging phenotypes (Reitz and Mayeux, 2009; Ritter and Bingel, 2009; Savitz and Drevets, 2009). Depending on the imaging modality, the intermediate imaging phenotype may indicate a genetic influence on regional variation in brain structure, on the distribution of neuronal activity or on distinct metabolic processes such as neuroreceptor function. Ultimately, intermediate imaging phenotypes from several imaging modalities need to be combined to fully capture the impact of genetic risk variants on different neurobiological aspects of brain function and structure, for instance by combining PET of regional neurotransmission with BOLD fMRI during an experimental task (Heinz et al., 2003). Although such a strategy requires substantial resources and poses methodological challenges, multimodal phenotyping may be more revealing given the multiple mechanistic links between genotype and phenotype (Meyer-Lindenberg et al., 2005).

NEUROIMAGING IN MONOGENIC NEUROPSYCHIATRIC DISORDERS

An equally important neuroimaging-genetics approach takes a more clinical perspective focusing on specific neurogenetic disorders. Brain imaging of individuals carrying a mutation associated with a neurogenetic syndrome provides a unique opportunity to link a specific genetic alteration to aberrant brain structure, thereby narrowing the gap between basic genetic research and a pathological or clinical understanding of these diseases. In the last decade, the number of genetic alterations that have been identified to cause hereditary neuropsychiatric disorders has dramatically increased, although this has not extended as of yet to the more common diseases of complex heritability. Furthermore, molecular and cellular neurobiology has produced a steadily growing wealth of knowledge about the molecular and cellular function of the affected genes and how these functions are altered by the mutation. This renders the task of linking genes to brain function and behaviour more straightforward for genes harbouring disease-causing mutations than for genes harbouring functional variants. In this issue, Walter et al. (2009) argue for combined analyses of multimodal neuroimaging data across neurogenetic conditions to delineate common organizing principles in development. They illustrate this point by reviewing the behavioural and neuroimaging studies of visuospatial processing abilities in Williams, Fragile X, Turner and velocardiofacial syndromes. These studies revealed a shared set of deficits in visuospatial processing across these neurogenetically heterogeneous syndromes, suggesting a common pathophysiological link.

Three contributions in this special issue highlight the potential of imaging genetics in hereditable movement disorders of monogenic origins. Huntington's disease is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion in the gene encoding the protein huntingtin. The contribution by Klöppel et al. (2009) summarizes recent structural and functional MRI studies in Huntington's disease. In Huntington's disease, there is a

need to monitor the effects of neurodegeneration in individuals over time to evaluate degeneration-modifying treatments. Klöppel et al. (2009) discuss the potential role of structural MRI as a biomarker of disease progression for clinical therapeutic trials. Here, MRI could be used to stratify affected individuals by the degree of caudate atrophy, especially in the pre-symptomatic stage, resulting in more homogeneous populations. Carbon and Eidelberg (2009) review the use of multimodal neuroimaging in individuals with mutations in the DYT1 or DYT6 gene. Mutations in both genes are associated with autosomal dominant dystonia. Clinical penetrance is incomplete in both conditions. Neuroimaging of manifesting and non-manifesting mutation carriers provides valuable pathophysiological links between gene carrier status and clinical penetrance by identifying genotype-related (penetrance-independent) neuroimaging traits and phenotype-specific (penetrance-related) changes in brain function and structure (Carbon and Eidelberg, 2009). Another promising area of imaging genetics in the field of movement disorders has been fuelled by the discovery of mutations in single genes that can cause autosomal dominant or recessive Parkinson's disease (PD). In this issue, van der Vegt et al. (2009) review how multimodal neuroimaging of individuals carrying a mutation in one of these PD-associated genes can be used to tap into the pathogenesis of parkinsonism. In particular, they show that neuroimaging research in non-manifesting mutation carriers can identify mechanisms of adaptive reorganization in the preclinical stage of PD. They also summarize recent work that has started to explore how functional SNPs in the dopaminergic signaling pathway impact on dopamine related cognitive processing and its modification by dopaminergic therapy in PD.

CONCLUSIONS AND OUTLOOK

As outlined above, a strong focus on advancing phenomics is needed to develop more sophisticated and appropriate methods to assay the phenotypes of interest (Bilder et al., 2009). It is clear that many traits may vary over time and this in turn would be subject to genetic regulation in addition to environmental factors (Bougnères, 2003). These dynamics of imaging phenotypes can only be captured in longitudinal studies with repeated imaging sessions so that we do not miss important modifying effects of time on genetic association. For example, the maturation trajectory of the corticospinal tract, a learning-related change in brain activity during the acquisition of a manual skill or a disease-related expression of a metabolic network may be considered as state-sensitive imaging phenotypes (Carbon and Eidelberg, 2009; Cheeran et al., 2009). Neither can we ignore mapping the dynamics of state-sensitive phenotypes in imaging genetics. First, while genetic studies often deal with lifelong aberrations of expression or function, patients are treated in real time and it is these changes in state that often drive drug development (e.g., symptomatic control of psychosis or reduction in frequency of depression) and rehabilitation protocols. For example, it would be wise to understand the relationships between traits under study and states we wish to manipulate clinically. While eliminating those state phenotypes ill-suited for genetic study, we might uncover in these state-trait relationships previously obscured phenomena linked to specific neurobiological mechanisms such as maturation or activity-driven plasticity which are likely to have genetically-driven components. Moreover, state-trait relationships and distinctions will be important to the still maturing field of identifying quantifiable gene–environment-interactions. For instance, variations in the state–trait relationships between imaging factors may uncover the genetic and environmental vulnerability (or resilience) to complex neuropsychiatric disorders.

State-dependent imaging phenotypes can be studied using a perturb-and-measure-approach (Cheeran et al., 2009; Savitz and Drevets, 2009). A wide range of "perturbations" are at hands to experimentally change the state of the brain and uncover phenotypic state-dependency, comprising pharmacological challenges, behavioural interventions (e.g., placing individuals under stress, ask them to practice a learning task for a prolonged period) or interventional neurostimulation (e.g. deep brain stimulation, cortical stimulation). However, the perturb-and-measure-approach is more costly and time-consuming, limiting its large-scale application in sufficiently large populations.

The ongoing advances in neurogenetics will have a major impact on future study designs in the field of imaging genetics. New analytic methods and declining costs will prompt the use of finer grained methods to map the human genome, including the detection of rare variants and copy number variations. This will require even larger sample sizes to detect robust genetic associations with complex multi-level phenotypes (Bilder et al., 2009). Concurrently, this will pose unprecedented challenges for computational neuroscience. New neuroinformatics tools will have to be developed that can interrogate the highly multi-dimensional datasets acquired at multiple biological scales and can sufficiently capture the enormous genomic and phenomic complexity.

Another challenge is to further develop epigenomics to clarify the contribution of epigenetic factors to individual variations in complex phenotypes beyond variance explained by genomic data (Bilder et al., 2009). Epigenetic inheritance refers to the regulated pattern of gene expression inherited from one or the other parent to their offspring independent of DNA informational content.

Finally, it will be crucial to implement animal models in the research strategy (Casey et al., 2009; Klöppel et al., 2009). Imaging genetics in humans greatly benefits from parallel research in genetic mouse models that mimic the human polymorphism, making a strong case for research that "moves back and forth between the human and the mouse" (Casey et al., 2009; Klöppel et al., 2009). This vertical research strategy operates top down in humans, from the level of syndromes through symptoms and imaging phenotypes to neural systems, and bottom-up in mice by establishing new transgenic models and examining the effects of the genetic manipulations on molecular expression, cellular signaling pathways, and neural systems (Bilder et al., 2009).

In summary, advances in neuroimaging and genomics provide an unprecedented opportunity to unravel the neu-

robiological mechanisms underlying neuropsychiatric diseases and normal variation in cognition and behaviour. This issue illustrates recent advances, challenges and implications of linking genetic variance to structural and functional variation in human brain systems. It is safe to state that the synergism of integrating genetics with brain imaging will dramatically change our understanding of human brain function in health and disease. However, the emerging field of imaging genetics in humans faces manifold inter-disciplinary challenges which have to be met to fully realize its synergistic potential.

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